

Simultaneously targeting Bcl-2 and Akt pathways reverses resistance of nasopharyngeal carcinoma to TRAIL synergistically

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ABSTRACT

Aims and background. Despite progress in treatment techniques, the five-year survival rate of nasopharyngeal carcinoma (NPC) is disappointing. Tumor necrosis factor-related apoptosis inducing ligand (TRAIL) can selectively induce apoptosis in most tumor cells while sparing normal cells. Given the antiapoptotic functions of Bcl-2 and Akt, we examined the effects of targeting these pathways alone or simultaneously on TRAIL apoptosis in NPC cell lines.

Methods and study design. We first tested the cytotoxic effect of TRAIL and the expression of death receptors, Bcl-2, Akt, and p-Akt on four NPC cell lines by MTT and Western blotting, respectively. Small interfering RNAs (siRNAs) targeting Bcl-2 and PI3-K inhibitor (LY294002) were used alone or combined with TRAIL in the cell lines and cytotoxicity was examined by MTT. Apoptosis rates, mitochondrial transmembrane potential, and apoptotic pathway signals were detected by flow cytometric analysis, DiOC6(3) assays, and Western blotting after the various combination treatments on CNE-2, the cell line that was most resistant to TRAIL.

Results. Although no direct correlation between the sensitivity to TRAIL and the relative expression levels of Bcl-2 and activated Akt was found in the NPC cell lines examined, siRNA mediated the downregulation of Bcl-2 and LY294002-induced inactivation of Akt, increasing the sensitivity of all examined NPC cell lines to TRAIL. Synergistic enhancement of TRAIL-mediated cytotoxicity was observed in combination treatment of Bcl-2 siRNA and LY294002 compared to cells treated with each treatment alone. The synergistic effects were mediated through increased apoptotic signaling of the mitochondrial pathway, as was evident from the more increased mitochondrial depolarization, activation of caspase-9 and caspase-3, and suppression of XIAP.

Conclusions. This study provides proof of principle that TRAIL combined with simultaneously targeting the Bcl-2 and Akt signaling pathways may have potential as a novel future treatment strategy for NPC.

Key words: nasopharyngeal carcinoma, TRAIL, resistance, Bcl-2, Akt.

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